MedicalXpress

Findings to help in design of drugs against virus causing childhood illnesses

March 21 2013, by Emil Venere

New research findings may help scientists design drugs to treat a virus infection that causes potentially fatal brain swelling and paralysis in children.

The virus, called enterovirus 71, causes hand, foot and mouth disease and is common throughout the world. Although that disease usually is not fatal, the virus has been reported to cause fatal encephalitis in infants and young children, primarily in the Asia-Pacific region.

Currently, no cure exists for the infection.

New findings show the precise structure of the virus bound to a molecule that inhibits infection. The findings are detailed in a paper appearing this week in *Proceedings of the National Academy of Sciences*.

"These results provide a structural basis for development of drugs to fight enterovirus 71 infection," said Michael G. Rossmann, Purdue University's Hanley Distinguished Professor of Biological Sciences.

Rossmann is co-author of a paper with Purdue postdoctoral research associate Pavel Plevka; research scientist Rushika Perera; postdoctoral research associate Moh Lan Yap; Jane Cardosa, a researcher at Sentinext Therapeutics in Malaysia; and Richard J. Kuhn, a professor and head of Purdue's Department of Biological Sciences.

The researchers had previously used a technique called X-ray

crystallography to determine the virus's precise structure. A small molecule called a "pocket factor" is located within a pocket of the virus's protective shell, called the capsid. When the virus binds to a human cell, the pocket factor is squeezed out of its pocket resulting in the destabilization of the virus particle, which then disintegrates and releases its genetic material to infect the cell and replicate.

Researchers led by Rossmann have developed antiviral drugs for other enteroviruses such as rhinoviruses that cause the common cold. The drugs work by replacing the pocket factor with a molecule that binds more tightly than the real pocket factor, inhibiting infection. In the new work, the researchers obtained a near-atomic-scale resolution three-dimensional structure of enterovirus 71 binding with an inhibitor called WIN 51711.

"We show that the compound stabilizes the virus and limits its infectivity, probably through restricting dynamics of the capsid necessary for genome release," Rossmann said. "Our results provide a structural basis for development of antienterovirus 71 capsid-binding drugs."

At a resolution of 3.2 angstrom, the images show nearly atomic-scale structural features.

Hand, foot and mouth disease, an infection most common among young children, sometimes arises in a daycare setting. Of the 427,278 cases of the disease recorded in mainland China between January and May 2010, 5,454 cases were classified as severe, with 260 deaths, according to the World Health Organization.

More information: Structure of Human Enterovirus 71 in Complex with a Capsid-Binding Inhibitor, *Proceedings of the National Academy of Sciences*, 2013.

Human enterovirus 71 is a picornavirus causing hand, foot and mouth disease that may progress to fatal encephalitis in infants and small children. As of now, no cure is available for enterovirus 71 infections. Small molecule inhibitors binding into a hydrophobic pocket within capsid viral protein 1 were previously shown to effectively limit infectivity of many picornaviruses. Here we report a 3.2-Å-resolution X-ray structure of the enterovirus 71 virion complexed with the capsid-binding inhibitor WIN 51711. The inhibitor replaced the natural pocket factor within the viral protein 1 pocket without inducing any detectable rearrangements in the structure of the capsid. Furthermore, we show that the compound stabilizes enterovirus 71 virions and limits its infectivity, probably through restricting dynamics of the capsid necessary for genome release. Thus, our results provide a structural basis for development of antienterovirus 71 capsid-binding drugs.

Provided by Purdue University